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The Effects of Exercise on Success Rates of In Vitro Fertilization

Abstract

Background: In the United States, 2.3% of women of childbearing age seek treatment for infertility, many of which require the use of in vitro fertilization. Women beginning this therapy are highly motivated to improve their overall health and often engage in diet and exercise modifications. It is well studied that women who engage in strenuous exercise regimens encounter anovulation, hormonal fluctuations, and disturbed energy balance, all of which decrease fertility. Alternately, overweight and obese women who do not exercise also experience infertility and an increased rate of miscarriage, which decrease with weight loss from improved diet and exercise. New research suggests that exercise intensity and duration are important considerations for women preparing for IVF, as strenuous exercise has the potential to reduce the success of IVF outcomes in all women, regardless of BMI.

Method: An exhaustive search was conducted using Medline-OVID, CINAHL (EBSCO Host), and Web of Science using the keywords: "Fertilization in Vitro," "exercise," "infertility," "obesity," and "lifestyle." The reference list of each relevant article was scanned for additional pertinent studies. Each selected article was assessed for quality using GRADE.

Results: Two studies met inclusion criteria and were included in this systematic review. A randomized controlled pilot trial with 38 participants demonstrated an increase in live birth and decrease in pregnancy loss among overweight women undergoing IVF who engaged in mild to moderate walking based exercise program. A prospective observational study with 2232 participants demonstrated a statistically significant reduction in live births and increase in pregnancy loss, fertilization failure, implantation failure and cycle cancellation in women who engaged in cardiovascular exercise for greater than four hours per week for one to nine years prior to their first IVF intervention.

Conclusion: Mild to moderate exercise in overweight individuals is shown to improve the outcome of an IVF cycle. Conversely, strenuous cardiovascular exercise may show a decrease in live births and increase in pregnancy loss in all BMI categories. Women preparing for IVF should not initiate a new cardiovascular exercise program close in time to initiation of an IVF cycle, but mild to moderate walking based programs are not observed to cause harm. A weak recommendation that providers should caution against strenuous exercise for women who are preparing for IVF cycles is offered.

Keywords: Fertilization in Vitro, exercise, infertility, obesity, and lifestyle

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The Effects of Exercise on Success Rates of In Vitro Fertilization

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Biography

[Redacted for privacy]

Abstract

Background: In the United States, 2.3% of women of childbearing age seek treatment for infertility, many of which require the use of in vitro fertilization. Women beginning this therapy are highly motivated to improve their overall health and often engage in diet and exercise modifications. It is well studied that women who engage in strenuous exercise regimens encounter anovulation, hormonal fluctuations, and disturbed energy balance, all of which decrease fertility. Alternately, overweight and obese women who do not exercise also experience infertility and an increased rate of miscarriage, which decrease with weight loss from improved diet and exercise. New research suggests that exercise intensity and duration are important considerations for women preparing for IVF, as strenuous exercise has the potential to reduce the success of IVF outcomes in all women, regardless of BMI.

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Conclusion: Mild to moderate exercise in overweight individuals is shown to improve the outcome of an IVF cycle. Conversely, strenuous cardiovascular exercise may show a decrease in live births and increase in pregnancy loss in all BMI categories. Women preparing for IVF should not initiate a new cardiovascular exercise program close in time to initiation of an IVF cycle, but mild to moderate walking based programs are not observed to cause harm. A weak recommendation that providers should caution against strenuous exercise for women who are preparing for IVF cycles is offered.

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List of Abbreviations

IVF	In Vitro Fertilization
LH	Luteinizing Hormone
FSH	Follicle Stimulating Hormone
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
NNT	Number Needed to Treat

Exercise and In Vitro Fertilization: Friend or Foe?

BACKGROUND

In the United States alone, 7.3 million women between the ages of 15-44 (11.8%) have sought treatment for infertility.¹ Of those women who elected to use In Vitro Fertilization (IVF), the causes of infecundity varied, however, the most significant were tubal factor, male factor, endometriosis, unexplained infertility, and polycystic ovarian syndrome.² As this technology is costly both monetarily and emotionally, women undergoing IVF are shown to be more motivated to implement healthy lifestyle routines, including diet and exercise, in an attempted to increase success of treatment.³

It has been well documented that women who engage in strenuous exercise regimens encounter anovulation, hormonal fluctuations, and disturbed energy balance, all of which decrease fertility. Specialists have discovered that the primary dysfunction caused by exercise is luteal phase abnormality, yielding either a shortened luteal phase with a decrease in total luteinizing hormone (LH) release, or by a delay in the occurrence of the LH surge. This seemingly minor alteration in the hormonal milieu can lead to a decrease in the total progesterone secretion, leaving the endometrial lining insufficiently thick and thus inhospitable to implantation of a fertilized embryo.⁴

Conversely, overweight and obese women who do not exercise, also experience infertility and an increased rate of miscarriage. The suspected mechanism is alterations in the secretion of gonadotropin releasing hormone, LH, and ovarian and adrenal hormones, causing anovulation, decreased follicular progression, decreased embryonic development, and implantation failure.^{2,5} An additional concern in overweight women is insulin

resistance, which can unfavorably impact reproductive function.⁴ Overweight and obese women with a BMI greater than 25 have also been shown to have decreased chance of pregnancy when using IVF technologies when compared to women with a BMI less than 25.⁶ Weight loss through lifestyle modifications has been shown to positively influence the rate of live births in overweight women who conceive with or without the use of assisted reproductive technologies.⁷

Recent research, however, has shown that encouraging lifestyle modifications prior to the initiation of an IVF treatment cycle may be controversial. Though exercise can generally be considered beneficial for overall health and disease prevention, moderately intense cardiovascular exercise initiated in close proximity to a conception period, may actually decrease the success of IVF.⁸ It is curious to note that patients with higher starting body mass indices (BMI) have improved implantation, an increased chance of pregnancy, and a decreased the risk of miscarriage when mild to moderate physical activity is combined with IVF therapy,⁹ while women with normal or lower BMIs may have decreased success with the same treatment.^{5,8} Thus, health care providers must be cognizant of the detriments prior to recommending an exercise program for patients preparing for IVF.

METHOD

An exhaustive search of medical literature available through online databases and the Pacific University library was conducted using Medline-OVID, CINAHL (EBSCO Host), and Web of Science using the keywords “Fertilization in Vitro,” “exercise,” “infertility,” “obesity,” and “lifestyle.” Articles were excluded if they were not in the English language or if subjects were non-human. Listed citations of relevant articles were

further searched for additional sources. Only articles evaluating the impact of exercise on the outcomes of IVF were included. Selected articles were assessed for quality of research using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.¹⁰

RESULTS

After combining terms “Fertilization in Vitro” and “exercise,” the resulting search yielded 10 articles for review. After screening for relevancy, two articles satisfied inclusion criteria. These articles include one prospective observational study⁸ and one randomized controlled pilot study.³ See Table 1.

Morris et al

This prospective observational study⁸ focused on how different exercise type, duration, and intensity impacted women preparing for their first cycle of In Vitro Fertilization. A total of 2232 women who were attending one of three IVF clinics in the Boston, Massachusetts area were enrolled between 1994 and 2003. The data was collected from a questionnaire administered prior to the patients undergoing treatment. The primary outcomes measured were live birth, pregnancy loss, implantation failure, failed fertilization, and cycle cancellation. Of these women, 859/2232 reported no exercise participation. Those who did report regular exercise were divided into four categories of exercise duration. These four categories were numbered one through four and detailed as follows: Category 1; 1-3 hours per week for 1-9 years (n=221), Category 2; 4 or more hours per week for 1-9 years (n=230), Category 3; 1-3 hours per week for 10-30 years (n=352), Category 4; 4 or more hours per week for 10-30 years (n=502). Median age, gravidity, parity, and BMI were expressed for each category and no apparent

difference in baseline characteristics was observed. Data was also subcategorized by exercise type, detailed as walking, cardiovascular, and other. All patients who consented to complete the questionnaire were included and follow-up was complete for each participant. No follow-up was conducted beyond the results for each participants' first IVF cycle.⁸

Results showed that when compared to the 859 persons who reported no exercise, the compilation of 1368 persons who reported physical activity of any type for greater than one hour per week, there was a 20% lower likelihood of live birth, however, this was not statistically significant ($P=0.7$). Comparing these same groupings, there was a statistically significant 30% increase in implantation failure in women who exercised regularly ($P= 0.04$).⁸

The most notable result was observed once the individuals reporting physical activity were subcategorized by duration. Women in Category 2 (see above description) had a 40% decreased likelihood of a live birth after the first cycle of IVF as compared to non-exercisers. Additionally, the women in this category were nearly three times more likely to have cycle cancellation (OR 2.8, CI 1.5-5.3), twice as likely to experience implantation failure (OR 2.0, CI 1.4-3.1), and pregnancy loss (OR 2.0, CI 1.2-3.4) than non-exercisers. The fertilization failure rate was unchanged between exercise category 2 and non-exercisers. The remaining three exercise categories (1,3,4) showed no significant differences in outcome compared to non-exercisers. When researchers stratified by BMI categories set forth by the World Health Organization instead of exercise duration, they did not find a statistically significant difference between exercise and IVF outcome.⁸

When data was analyzed by type of exercise, there was also a significant result. Women who engaged in cardiovascular exercise were 30% less likely to have a successful live birth (OR 0.7, CI 0.6-0.9). When data was subcategorized further to cardiovascular exercisers of Category 2 duration, the results were more noteworthy. There was a 50% decreased likelihood of live birth (OR 0.5, CI 0.3-0.8), five times increase in cycle cancellation (OR 5.1, CI 2.3-11.5), and approximately two and a half times increase in implantation failure (OR 2.6, CI 1.5-4.6) and two and a half times increase in pregnancy loss (OR 2.4, CI 1.1-4.9) as compared to non-exercisers. Of cardiovascular exercisers of Category 3 duration, there was a 40% (OR 0.6, CI 0.4-1.0) reduction in live birth observed as compared to non-exercisers. Though the general walking category showed no difference as compared to non-exercisers in terms of live birth rate, when Category 2 duration walkers were analyzed, there appeared to be a 50% reduction in successful live birth as compared to non-exercisers.⁸ See Table 2.

Moran et al

In this randomized controlled pilot study,³ the authors were investigating the impact of short-term weight loss in overweight or obese women on the outcome of IVF cycles. A total of 46 women were selected to participate, all of who had a BMI greater than or equal to 28, were between the ages of 18 and 40 years, and were preparing to undergo IVF in Adelaide, Australia. None of the women had polycystic ovary syndrome and all had previously undergone at least one IVF cycle. Eight women dropped out of the study, three from the active treatment group and five from the control group; this left eighteen women to continue with active treatment and twenty women in the control group. Women consented to participate prior to beginning their IVF cycle and were then

randomized by a computer-generated sequence to active dietary modification and exercise or to the standard treatment control group. There were no differences in baseline characteristics between the two groups.³

Women in the active treatment group would be administered a specific nutritionally sufficient reduced energy diet in addition to a home-based physical conditioning and walking regimen. These women would have one initial visit with a certified dietician, a face-to-face follow up after two weeks, and a phone call follow-up one month from the initiation of the program. The diet and exercise program were continued until oocyte retrieval, at which time all women discontinued the exercise portion, but continued the diet until embryo transfer at which time all intervention ceased. The total treatment period spanned from five to nine weeks prior to oocyte retrieval. Individuals randomized to the standard treatment group had one face-to-face meeting with a dietician, who offered general suggestions on suitable diet and lifestyle recommendations, with no specific guidelines or programs and no active follow-up on progress. Measurements of weight, BMI, and waist circumference were obtained for all women prior to initiation of treatment and again at the time of embryo transfer.³

Though both the active and control groups showed a statistically significant decrease in waist circumference, only the active group showed reductions in weight and BMI. Because of the very small sample size, the authors could not conclude that there was a significant difference in the number of live births, though the calculated relative risks and actual proportions of live births appeared to be quite improved in the active group (7/18, 38.9%, RR 1.56) who showed weight and BMI reduction when compared with the control group (5/20, 25%) who did not show any improvement in weight or

BMI. The authors calculated that in comparison to the expected spontaneous pregnancy rate of <10% per month, the moderate energy-restricted diet combined with the moderate exercise program actually increased the rate of pregnancy to 53%. Individuals who had decreased waist circumference in either category did have an increased rate of becoming pregnant, but not necessarily with an outcome of live birth.³ See Table 2.

The authors noted that the individuals within the control group were not necessarily non-exercisers. These individuals were advised by a health care provider as to lifestyle modification, but were not offered a specific plan of diet or exercise to follow. This is significant because it is likely that they also engaged in some form of diet and exercise modification on their own, it was just not specifically reported or detailed. This group did yield a significant reduction in their waist circumferences, which according to the authors, exhibited the highest correlation to improving chances of becoming pregnant though no change to their weight or BMI was seen.³

DISCUSSION

The data presented above is of interest to the medical community because it throws into doubt the universal recommendation to exercise given to patients preparing for IVF therapy. The Morris et al study⁸ showed that, whether the body mass index of IVF patients was classified as underweight, normal, overweight, or obese, strenuous exercise decreased the incidence of successful live birth and increased the incidence of pregnancy loss. The Category 2 exercisers who showed the most harm done by exercise comprised BMIs from 19.6 to 33.0 and authors state that even when this group was stratified for BMI, there was no statistically significant difference in outcome. It should

then be recommended that though lifestyle choices can contribute to overall health, patients of any weight should avoid strenuous exercise prior to IVF.

Though the female athlete triad is well understood as preventing ovulation and altering hormonal production,¹¹ its deleterious impact on other specific facets of an IVF pregnancy have not been well documented. From Morris et al,⁸ it is observed that exercise is not likely to cause harm in women undergoing IVF if it is of low intensity and performed for less than three hours per week, or when continued (even when strenuous) for longer than ten years. Both physical and physiological stress inevitably alter LH secretion, thus initiating a training program a long time prior to beginning in vitro fertilization therapy will likely give the body more time to adapt to the stress placed upon it.¹¹ Exercise of a less strenuous nature, such as walking, may not influence the woman's hormonal milieu significantly enough to alter fertility, but may actually decrease adipose tissue, waist circumference, weight, and BMI, which may reduce the metabolic dysfunction that results in infertility in overweight persons.^{2,6} This suggests that women who are overweight prior to IVF therapy will likely have increased success with a weight-loss program including exercise, though this exercise should be only mild to moderate in intensity.

In vitro fertilization includes a downregulation of the hypothalamic-pituitary-ovarian axis through administration of exogenous hormones, including follicle stimulating hormone (FSH). The amount of FSH required for sufficient ovarian stimulation in women who are overweight or obese was increased as compared to women of a normal weight. This is indicative that weight plays a definitive roll in the body's receptiveness to hormone stimulation, explaining why infertility is not uncommon in

overweight or obese women to begin with. It has even been recommended that prior to attempting a pharmacological infertility treatment plan, women who are overweight or obese should begin reducing their weight as a first-line therapy to increasing body tissue receptiveness to endogenous hormones.¹²

As important as this research can be to medical practitioners, it is vital to note some of the limitations in the reviewed studies. In Morris et al,⁸ there is inherent recall bias when questionnaires are used and patients are asked to record their lifestyle habits over the last 1-30 years. Especially in a health care setting, patients have a tendency to misrepresent their lifestyle habits if they believe there are expectations as to what the provider hopes to hear.¹³ The authors of this study did not identify the causes of infertility of the participants, which could have been a profound confounder. Another shortcoming of this study was the subjective categories formed by the analysts. For example, Category 2 includes individuals who exercise for greater than four hours per week for 1-9 years. The spectrum is so broad, that it can include women who exercise four hours per week or ten hours per week, and those who've exercised consistently for only twelve months or as many as nine years. The author's categories of exercise type were also subjective. The walking group included only individuals who walked, while the cardiovascular group included jogging, running, aerobics, stair climbing, indoor rowing, elliptical treadmill, cross-country skiing or bicycling. Activities in the "other" group were swimming, racquet sports, team sports, yoga, weight lifting, or martial arts. Many team sports incorporate cardiovascular exercise during both games and conditioning training, though they were not included in the evaluation of the cardiovascular group when data was examined. This study only gathered information from patients prior to initiation of the IVF cycle, so

exercise routines may have changed after the collection of information, which could have positively or negatively influenced the outcome.⁸

The Moran et al study³ also exhibited several limitations. There was no blinding of researchers to treatment allocation; evaluators were aware to which group participants belonged, as they were the ones to administer the interventions. One major shortcoming was that the specific program of lifestyle change enacted, was not set forth in the article, though it was taken from The CSIRO Total Wellbeing Diet Book 1, which is available for purchase on the internet. The intensity, and duration of exercise engaged in by the active group is not detailed, though it is stated that it was walking based. An additional concern is that the exercise and diet modifications of the standard or control group were not elaborated upon, and it is possible that members of the control group also purchased The CSIRO Total Wellbeing Diet Book 1 and took their regimen from its program. They could have implemented very little change, or begun very intense programs for wellness either of which could have produced the results seen. It is difficult to compare the progress of two groups when the action taken by the control group is entirely unknown. This missing information is significant because there was an observed change in waist circumference in both active and control groups, but with no known cause in the control group. Because this randomized controlled trial was a pilot study, the sample size was very small; only 46 participants were enrolled and after eight withdrew, the total number of subjects studied was 38. This is not considered to be a sufficient sample size to draw definitive conclusions regarding treatment, only preliminary evidence may be taken from this data. The purpose of this study was to provide future researchers with information as to selecting a sufficient sample size.³

Both studies were assessed using GRADE and Morris et al⁸ was given a quality appraisal of very low while Moran et al³ was given a quality appraisal of low. Morris et al began at a low quality score because it is a prospective study and was further downgraded because of the potential for recall bias and poorly controlled confounding variables. There was no serious indirectness, imprecision, inconsistencies, or publication bias identified. Moran et al began at a quality score of high because it was a randomized controlled trial, but was downgraded due to the lack of blinding and the sample size was small because the trial was a pilot study. There was no publication bias likely and no serious inconsistencies were identified.

Though future studies into the impact of exercise on the success of IVF will be vitally important in clarifying what guidelines medical providers should offer patients preparing for this treatment, there appears to be potential for harm, thus a randomized control setting may not be considered ethical. If observational studies ensue, they should be well structured and include close monitoring of patients behavior so data is as accurate as possible. All precautions should be made to avoid recall bias and a treatment plan should be well outlined for both active and control groups.

The data collected from these studies certainly do not suggest a shift to sedentary lifestyle for women preparing for IVF, however, providers should consider advising against strenuous cardiovascular exercise. More data is needed to outline new guidelines for this particular population subset, but until that time, health care providers may recommend weight loss for overweight IVF patients so long as only mild to moderate intensity exercise is practiced.¹⁴ The data do not clearly demonstrate that there is an obvious relationship with duration of activity and a harmful outcome.

CONCLUSION

Though exercise is shown to generally improve health, it can be detrimental to some women who are preparing to undergo In Vitro Fertilization. More specifically, the evidence supports mild to moderate exercise in overweight individuals to improve the outcome of an IVF cycle, but conversely may show a decrease in live births and increase in pregnancy loss when strenuous cardiovascular exercise is initiated close in time to in vitro procedures and occurs for greater than four hours per week in all BMI categories. Women preparing for IVF should not initiate a new cardiovascular exercise program when preparing for IVF, but mild to moderate walking based programs are not shown to cause harm. Additional research to explore the mechanism behind this phenomenon should be undertaken, but until definitive proof is available, a weak recommendation that providers should caution against strenuous exercise for women who are preparing for IVF cycles is offered.

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TABLES

Table 1: GRADE evidence profile: Exercise and Impact on IVF

Quality Assessment											
Study Detail		Downgrade Criteria					Upgrade Criteria			Quality	Comments
Participants	Design	Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely	Large effective Magnitude	Confounding Factors reducing effect	Dose-response gradient		
Effects of Lifetime Exercise on Outcome of In Vitro Fertilization (Morris et al) ⁸											
2232	Prospective	Recall Bias & Poorly Controlled Confounding	No serious indirectness	No serious imprecision	No serious inconsistencies	No bias likely	-	-	-	Very Low	No causes of infertility identified
Diet & IVF pilot study: Short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF (Moran et al) ³											
38	RCT Pilot	Lack of Blinding	No serious inderectness	Low sample size (PILOT STUDY)	No serious inconsistencies	No bias likely	-	-	-	Low	Control was non-specific advice to exercise rather than no exercise Weight loss didn't yield higher success rates, only waist circumference was significant across both groups No data on what caused waist circumference change in control group

Abbreviations: GRADE: Grading of Recommendations, Assessments, Development and Evaluation.
IVF: in vitro fertilization

Table 2: Summary of Findings: Exercise and impact of IVF

Summary of Findings																			
Live Birth				Pregnancy Loss				Fertilization Failure				Implantation Failure				Cycle Cancellation			
Critical				Critical				Important				Important				Important			
Exercise	Control	Relative Risk	NNT/NNH	Exercise	Control	Relative Risk	NNT/NNH	Exercise	Control	Relative Risk	NNT/NNH	Exercise	Control	Relative Risk	NNT/NNH	Exercise	Control	Relative Risk	NNT/NNH
Effects of Lifetime Exercise on Outcome of In Vitro Fertilization (Morris et al)																			
A	A	0.5 ^{B*}	A	A	A	2.4 ^{B+}	A	A	A	1.2 ^{B+}	A	A	A	2.6 ^{B+}	A	A	A	5.1 ^{B+}	A
Diet & IVF pilot study: Short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF (Moran et al)																			
7/18	5/20	1.56	7.14 (8)	5/12	3/8	1.11	25	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: GRADE: Grading of Recommendations, Assessments, Development and Evaluation.

*- This Odds ratio includes patients in the category 2 exercise group who also engaged in cardiovascular exercise combined. Category 2 exercisers of all intensities have an OR of 0.6 and cardiovascular exercise of all durations has an OR of 0.7.

+ This Odds ratio includes patients in the category 2 exercise group who also engaged in cardiovascular exercise combined. Category 2 exercisers of all intensities have an OR of 2.0 and cardiovascular exercise of all durations has an OR of 1.5.

+ This Odds ratio includes patients in the category 2 exercise group who also engaged in cardiovascular exercise combined. Category 2 exercisers of all intensities have an OR of 1.2 and cardiovascular exercise of all durations has an OR of 1.4.

+ This Odds ratio includes patients in the category 2 exercise group who also engaged in cardiovascular exercise combined. Category 2 exercisers of all intensities have an OR of 2.0 and cardiovascular exercise of all durations has an OR of 1.5.

+ This Odds ratio includes patients in the category 2 exercise group who also engaged in cardiovascular exercise combined. Category 2 exercisers of all intensities have an OR of 2.8 and cardiovascular exercise of all durations has an OR of 1.5.

A- The raw data and actual number of patients who experience each outcome was not provided by the authors

B- This is actually the Odds Ratio, rather than the relative risk as this was the data provided by the authors

C- This is actually the number needed to harm, as there were more lost pregnancies in the active group than in the control group